

REMARKS

Claims 1-6 are pending in the application. Claims 7-56 have been cancelled. Applicants have cancelled claims solely to advance prosecution and expressly reserve the right to file divisional applications or take such other appropriate measures deemed necessary to protect the subject matter in the canceled claims. Claim 4 has been amended to specify that the proteolytic site is added in the region between helices 3 and 4 of domain 1. Support for this limitation can be found in the specification, particularly for example: on page 18, lines 18-20; page 19, lines 1-3; and page 21, lines 6-19. No new matter has been added by way of amendment. Reexamination and reconsideration of the claims are respectfully requested.

The present invention was developed through extensive research and testing. As discussed, for example, in the specification on page 18, line 18 through page 19, line 11, the inventors analyzed the state of the art regarding the use of endotoxins. Then, based on extensive study of the structure and function of endotoxins (see page 16, line 8 through page 17, line 31), the inventors designed various types of modifications to endotoxins which improved their properties (see, *e.g.*, working Example 6 on pages 82-84 and working Example 7 on pages 84-85). Mutations of the invention include the addition of a protease-sensitive site or alteration of a protease-sensitive site (see page 19, lines 27-29) as well as mutations that protect the endotoxin from protease degradation (see page 22, lines 25-28). The mutations may be used singly or in any combination (see page 19, lines 10-11).

Applicants have provided working examples to demonstrate the improved properties of endotoxins containing the claimed modifications (see, *e.g.*, Example 6 on pages 82-84, Example 7 on pages 84-85, Example 8 on pages 85-88, Example 9 on pages 88-90, and Example 21 on pages 116-119, as well as the results shown in the Figures (see the figure legends on pages 6-8)). The specification provides additional support for the claim limitations. Particularly, the pending claims are drawn to an endotoxin comprising at least one engineered cathepsin-sensitive proteolytic site. Cathepsin-sensitive proteolytic sites are well known in the art, as discussed for example in the application on page 15, lines 17-19. Applicants have identified additional cathepsin-sensitive proteolytic sites, as discussed for example on page 23, line 27 through page 24, line 15. Accordingly, ample support exists for cathepsin-sensitive proteolytic sites.

The pending claims also include a functional limitation requiring that the endotoxin has improved pesticidal activity relative to an endotoxin which lacks said at least one cathepsin-sensitive proteolytic site. Pesticidal activity is defined on page 12, lines 15-20, and assays for pesticidal activity are discussed in the specification (*e.g.*, page 5, lines 3-12; page 42, lines 9-13; page 77, lines 20-22) and provided in working examples such as Examples 1 and 2 on pages 78-79, Examples 6 and 7 on pages 82-85, and Examples 8 and 9 on pages 85-90. The evaluation of endotoxins using such assays is well within the skill of those in the art, as illustrated by the experiments discussed in the working examples and references discussed and cited in the specification (*e.g.*, on page 77, lines 20-22).

Dependent claim 2 includes a limitation requiring the alteration of at least one other proteolytic site whereby the stability in an insect gut of said endotoxin is increased (see, *e.g.*, page 15, lines 9-11 and page 19, lines 7-9). Exemplary mutations providing such properties are discussed in the specification, for example, on page 24, lines 16-31. Working examples demonstrating the improved properties of endotoxins comprising these mutations are provided, for example, in Examples 8 and 9 on pages 85-90.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

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therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

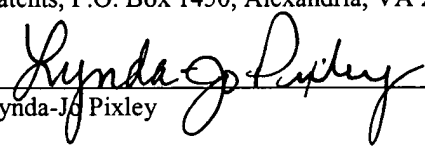


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